REMARKS

Claims 11, 12, and 14-31 are pending in the instant application. Claims 7-10 and 13 have been canceled without prejudice. Claims 12, 14 and 20-22 have been amended to correct claim dependencies. Claims 16 and 19 have been amended to correct certain typographical errors. No new matter has been added by these amendments.

Claim 12 has also been amended to recite a method for treating a patient suffering from breast cancer, cervical cancer, ovarian cancer, colorectal cancer or non-small cell lung cancer. Support for this amendment can be found throughout the specification, as well as in the previously submitted Declaration and supporting documents and the supporting documents submitted herewith.

Claims 23 to 31 are new. Support for new claims 23 to 31 can be found in the specification and claims as originally filed, including, but not limited to Paragraphs [0035] to [0047] of the corresponding U.S. Publication No. 2005/0249740. No new matter has been added.

The Specification has been amended to include the Section Titles requested by the Examiner on Pages 2-3 of the Office Action. The Specification has also been amended to include the required cross reference to related applications. This application is a U.S. National Stage application under 35 U.S.C. § 371 of International Application No. PCT/EP03/07415, filed July 9, 2003 which claims the benefit of German Application No. 103 05 531.2, filed February 11, 2003 and German Application No 102 30 875.6, filed July 9, 2002. The Application has been amended to reflect this.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is believed to be in condition for allowance.

Priority

The Examiner has acknowledged Applicants' claim for foreign priority under 35 U.S.C. 119(a)-(d) and receipt of the foreign priority papers but has requested the priority claim be completed by including a cross reference to the related applications in the specification and by providing a certified English translation of the foreign applications.

To that end, Applicants have amended the specification to include the required cross reference and submit herewith verified English translations of German Application No. 103 05 531.2 and German Application No 102 30 875.6, each of which have been certified as true and correct translations.

Applicants respectfully request reconsideration of the award of priority.

Claim Objections

Claim 7 has been objected to as comprising typographical informalities. Claim 7 has been canceled without prejudice. As such, the objection is moot.

Claims 16 and 19 have been objected to as comprising typographical informalities. As amended herein, the typographical informalities have been corrected. No new matter has been added. Applicants thank the Examiner for such careful examination of the claims.

Claim 13 has been objected to as being in improper dependent form. Without conceding the validity of the Examiner's objection, claim 13 has been canceled without prejudice.

Claims 8, 12, and 14-19 have been objected to as being in improper dependent form. Claim 8 has been canceled without prejudice. Claim 12 and 14-19 have been amended such that they each depend from new claim 23 either directly or indirectly. Applicants' believe that new claim 23 is fully defined and described and that such rejection is now moot.

Applicants respectfully request that the objections to the claims be withdrawn.

Rejections under 35 U.S.C. §112 , first paragraph

Claims 7, 9, 10 and 12 are rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement.

While Applicants strongly disagree with the Examiner's allegation, and solely for the purpose of advancing prosecution, Claims 7, 9 and 10 have been canceled without prejudice. As such, the rejection to these claims is moot.

Similarly, while Applicants disagree with the Examiner's allegation regarding the Claim 12, Applicants have amended Claim 12 to recite a method for treating a patient suffering from breast cancer, cervical cancer, ovarian cancer, colorectal cancer or non-small cell lung cancer. Applicants respectfully submit that the experimental data provided in the previously submitted declaration of Dr. Dömling as well as the poster cited therein and the correlation with the supplemental supporting material submitted herewith, demonstrates a correlation between the instantly claimed compounds and methods and, *at a minimum*, the cancer cell lines disclosed in the declaration as well as those of the supporting references references. As such, Applicants assert that the instantly claimed methods are fully enabled.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 112, First Paragraph be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claim 7 has been rejected under 35 U.S.C. § 112, Second Paragraph as being indefinite with respect to the variable R^{16}. As stated above, Claim 7 has been canceled without prejudice.. As such, the rejection is moot.

Claims 20-22 are rejected under 35 U.S.C. § 112, Second Paragraph as being indefinite with respect to the subject matter of the preamble. Applicants have respectfully amended claims 20-22 to depend from claim 16 – a method claim. No new matter has been added by this amendment. As such, Applicants believe claims 20-22 are sufficiently definite for the purposes of 35 U.S.C. § 112, Second Paragraph.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 112, Second Paragraph be withdrawn.

Rejections under 35 U.S.C. §102(a/e)

Claims 7 and 8 are rejected under 35 USC § 102 (a/e) as allegedly anticipated by United States Patent Publication No 2002/0169125 to Leung ("Leung"). The Examiner alleges that Leung discloses a polyanionic polymer conjugated to a drug selected from the group tubulysin or dolastatin which exhibits cytotoxic properties and that the drug can be conjugated to the polyanionic polymer through an indirect linkage such as a bifunctional spacer.

As stated above, and without conceding the validity of the Examiner's rejection, Claims 7 and 8 have been canceled without prejudice and the rejection is therefore moot.

Nevertheless, as new claims 23-31, are directed to compounds bearing the same base formula as claim 7, Applicants will address the art with respect to new claim 23. New claims 23-31 are directed to specific derivatives which are linked to a polymer comprising a polyethylene glycol (PEG) with a specified point of attachment.

Leung is directed to recombinantly-produced polyanionic polymers, i.e. to bin-molecules as described in the instant priority application (DE 102 30 075.6). Leung only mentions tubulysins among a long list of possible drugs and does not disclose any example for a tubulysin linked to such a polyanionic polymer. As such, Applicants respectfully submit that nothing in Leung anticipates the claimed invention.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 102(a/e) be withdrawn.

Rejections under 35 U.S.C. §103(a)

Claims 9, 10 and 12-22 are rejected under 35 USC § 103 (a) as allegedly unpatentable over United States Patent Publication No 2002/0169125 to Leung ("Leung") in view of Greenwald *Journal of Controlled Release* 74, 159-171 ("Greenwald") and Duncan, 2001 *Journal of Controlled Release* 74, 135-146 ("Duncan").

The Examiner alleges that Leung discloses a polyanionic polymer conjugated to a drug selected from the group tubulysin or dolastatin which exhibits cytotoxic properties and that the

drug can be conjugated to the polyanionic polymer through an indirect linkage such as a bifunctional spacer.

As stated above, and without conceding the validity of the Examiner's rejection, Claims 9 and 10 have been canceled without prejudice and the rejection is therefore moot. Similarly, claims 12-22 now depend, either directly or indirectly on new claim 23 and thus the rejections with respect to these claims are also moot.

Nevertheless, as new claims 23-31, are directed to compounds bearing the same base formula as claim 7, Applicants will address the art with respect to new claim 23. New claims 23-31 are directed to specific derivatives which are linked to a polymer comprising a polyethylene glycol (PEG) with a specified point of attachment.

As discussed above Leung is directed to recombinantly-produced polyanionic polymers, i.e. to bin-molecules as described in the instant priority application (DE 102 30 075.6). Leung only mentions tubulysins among a long list of possible drugs and does not disclose any example for a tubulysin linked to such a polyanionic polymer. Furthermore, Leung only discloses the use of a polyanionic polymer to increase the water solubility and/or the half-life of the drug.

The present invention provides specific derivatives which are linked to a polymer comprising a polyethylene glycol (PEG) with a specified point of attachment. As described throughout the specification, the compounds of the instant claims lower the toxicity of a drug. Nothing in Leung describes the reduction in toxicity of a drug using the specific derivatives claimed. As such, even assuming for the sake of argument that one of ordinary skill in the art were to pick and choose the specific derivatives of the instant claims, one of ordinary skill in the art would have still lacked the required expectation of success in producing a compound with reduced drug toxicity.

Greenwald does nothing to rectify the deficiencies of Leung. As discussed in Applicants' prior responses, in the Rule 132 Declarations of record, it is shown that by coupling tubulysin A with a PEG ester, amide or phenol, the activity of the respective compounds in two cancer cell lines can be dramatically reduced, thus, leading to tubulysin derivatives with lower toxicity.

Furthermore, it is pointed out that Greenwald classifies PEG-drugs in permanently bonded PEG-drugs (cf. chapter 2, page 160) and non-permanently bonded PEG-drugs, i.e. PEG prodrugs (chapter 3, page 160).

According to Greenwald, permanently bonded PEG-drugs comprise PEG linkers of molecular weight 2000 to 5000, i.e. low molecular weight PEG. As can be taken from the Declaration filed November 30, 2006, tubulysin A PEG-derivatives having a PEG linker with high molecular weight, such as 35kDa or 40kDa provide better results with regard to the object of the present invention than low molecular weight PEGs. This finding is by no means rendered obvious by Greenwald suggesting to use permanently bonded PEG-drugs wherein the PEG linker has a molecular weight of from 2000 to 5000. On the contrary, Greenwald ***teaches away*** from the instant invention, further rebutting any case of *prima facie* obviousness contended.

As mentioned above, chapter 3 of the Greenwald publication, PEG prodrugs are disclosed. Greenwald states that a prodrug is a biologically inactive derivative of a parent drug molecule that usually requires an enzymatic transformation within the body in order to release the active drug, and has improved delivery properties over the parent molecule (cf. page 160, right-hand column, last paragraph). In other words, a prodrug is formed in order to render a parent drug molecule in a condition to enable absorption of the drug molecule in the human body. Once the prodrug has entered the human body, it is enzymatically transformed to release the active drug.

However, this scenario does not apply to the tubulysin derivatives according to the present invention. As stated in paragraph [0003] of the present specification, tubulysins possess an extremely high cytotoxicity. If the tubulysin derivatives released free tubulysins immediately after absorption in the human body, the free tubulysins would immediately exert their cytotoxic effects resulting in extensive cell death of normal cells. As a consequence, such tubulysin prodrugs are not selective and are connected with serious side effects. As stated in paragraph [0004] of the present specification, the object of the present invention is to enhance selectivity of tubulysins.

Applicant has surprisingly found that tubulysin derivatives according to claim 23 are stable in plasma/buffer and, thus, less cytotoxic than natural tubulysins as indicated above with regard to the experimental data set forth in the Rule 132 Declarations of record. Furthermore, Applicant has surprisingly found that once the tubulysin derivatives have entered a cancer cell, free tubulysin is released and can exert its high cytotoxic activity directly in the cancer cell. Accordingly, the compounds according to the present invention provide for drug targeting of

tubulysin selectively to cancer cells. These findings are by no means rendered obvious by the publications of Leung in combination with Greenwald.

Applicants' further submit a copy of Schluep et al. *Clin, Cancer Res*, 2009 15(1) 181-189, which discloses further experimental data of a tubulysin derivative which is linked to a polymer comprising PEG. As can be taken from the Schluep article and the poster attached to the previously submitted Declaration, tubulysin derivatives additionally comprising a cyclodextrin group provide additional benefits. In fact, cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells (cf, table 1), but are significantly less toxic than tubulysin A (cf. table 2). As evident from table 3 and graph 1, cyclodextrin conjugates of tubulysin are better tolerated than vinblastine and tubulysin A and lead to a significant increase in tumor growth delay, inhibit the formation of new tumor cells and at the same time reduce the number of existing tumor cells. It is again pointed out that the Leung publication does not pertain to tubulysin conjugates and that the Greenwald publication does not disclose cyclodextrin conjugates at all.

Similarly, Duncan does nothing to rectify the deficiencies of Leung nor Greenwald. Like Greenwald, Duncan does not disclose conjugates comprising a tubulysin derivative and a polymer comprising a PEG, Therefore, like Greenwald, Duncan cannot render the present invention obvious. In particular, Duncan does not disclose or suggest the conjugation of the specific tubulysin derivatives of formula (I) with a polymer comprising PEG via a linker at residue R^{19} or R^{20}.

As such, one of ordinary skill in the art would have no motivation to combine Leung, Greenwald and Duncan to arrive at the instantly claimed compounds and methods. As such, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

Double Patenting Rejection

Claim 7 was provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 19-32 of copending Application No. 10/520,793 in view of Leung.

As stated above, and without conceding the validity of the Examiner's rejection, claim 7 has been canceled without prejudice. As such, the double patenting rejection, while provisional, is moot. Applicants respectfully request that the double patenting rejections be withdrawn.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections, and allowance of the instantly claimed invention is earnestly solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at the telephone number below.

Applicants believe that there are no additional fees due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 04-1105 for any fee(s) due with this response.

Dated: May 19, 2009

Respectfully submitted,

Electronic signature: /Nicholas J. DiCeglie, Jr./
Nicholas J. DiCeglie, Jr.
Registration No.: 51,615
Edwards Angell Palmer & Dodge LLP
P.O. Box 55874
Boston, Massachusetts 02205
(212) 308-4411
Attorneys/Agents For Applicant

Customer No. 21874